Free Radical Methodology for Carbohydrate to Carbocycle Transformations: An Efficient Synthesis of the Tricyclic Dihydrofuran Portion of Azadirachtin[1]

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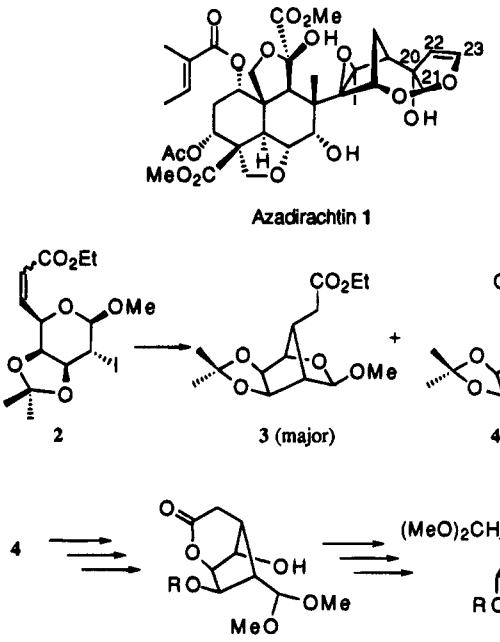
Summary: Iodo lactone **6b**, derived from D-galactal, undergoes tin hydride mediated transannular radical cyclization to give the tricyclic lactone **7**, which is easily converted into an advanced precursor of the tricyclic dihydrofuran portion of the potent insect antifeedant azadirachtin (**1**).

Strategies for preparing densely functionalized natural products or segments thereof from carbohydrate precursors are an area of interest in our laboratory.[2,3] These objectives provide a fertile ground for the development of free-radical methods which usually display high tolerance for the multiple functional groups being installed. Azadirachtin (**1**) (Scheme 1), the potent active principle of India's famed insecticidal neem tree,[4] is conveniently disconnected into *trans*-decalin and dihydrofuran acetal moieties, both of which may be categorized as densely functionalized carbocycles.

Previous reports from this group have shown that both the *E* and *Z* isomers of iodo-olefin **2** are cyclized under standard radical conditions to give bicyclic ester **3** along with minor amounts of its epimer **4** (Scheme 1).[2] It was envisioned that access to the minor isomer might allow for an expeditious approach to the bicyclic dihydrofuran segment of azadirachtin (**1**).[4] We herein report the successful realization of this goal by a key reaction which demonstrates that the stereochemistry of the critical radical cyclization (*i.e.*, **2** → **3**) can be reversed by constraining the radical acceptor as a lactone, thereby paving the way to a potential azadirachtin precursor.

The synthesis begins with selective production of (*Z*)-**2**, prepared by a modification of the method used previously (Scheme 2).[2] Commercially available D-galactal was subjected to thermodynamic acetonide[5] formation to give the known[6] 3,4-*O*-isopropylidenegalactal (**5**). Iodomethoxylation,[7] oxidation, and *Z*-selective Wittig olefination[8] gave (*Z*)-**2** in 60% yield. Treatment with TFA and water in toluene effected acetonide hydrolysis followed by slow lactonization to give a 75% yield of the bicyclic iodo-olefin **6a**. This material is relatively insoluble in many organic solvents used for radical reactions, but this was overcome with the use of the corresponding *tert*-butyldimethylsilyl (TBDMS) ether **6b**.

Scheme 1



The critical transannular cyclization was approached with uncertainty because of the strain that would be experienced by the tricyclic product. In the event, the crucial bond-forming reaction occurred smoothly when performed by slow addition of tri-*n*-butyltin hydride and AIBN to a dilute (5 mM) solution of **6b** in toluene at reflux to give the tricyclic lactone **7** in 87% yield as a crystalline solid.

Exposure of **7** to PPTS[9] in methanol at room temperature for 5 h gave a mixture of starting material and hydroxy acetal **8a** (**8a**:**7** = 6.8:1, 89%), in addition to small amounts of the anomeric 1-*epi*-**7**. Longer reaction times simply increased the proportion of the latter without improving the yield of **8a**. Radical deoxygenation of the extraneous hydroxyl group in **8a** via the *p*-fluorophenyl thionocarbonate **8b**[10] gave the bicyclo[3.2.1] lactone **8c** in 75% yield. This relatively simple enantiopure building block is available in eight steps and 24% overall yield from the monoacetone galactal **5**.

The C(20) oxygen (azadirachtin numbering) was introduced by hydroxylation of the potassium enolate of **8c** with the Davis oxaziridine,[11] and the α-hydroxy lactone **9a** was oxidized with PCC to the nonenolizable α-keto lactone **9b** in 70% yield (two steps). The remaining carbons necessary for installation of the dihydrofuran ring were introduced by lithium perchlorate catalyzed allylation of **9b** with allyltributylstannane in diethyl

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(1) We are grateful to the National Science Foundation (CHE 9311356) for financial support of this work.
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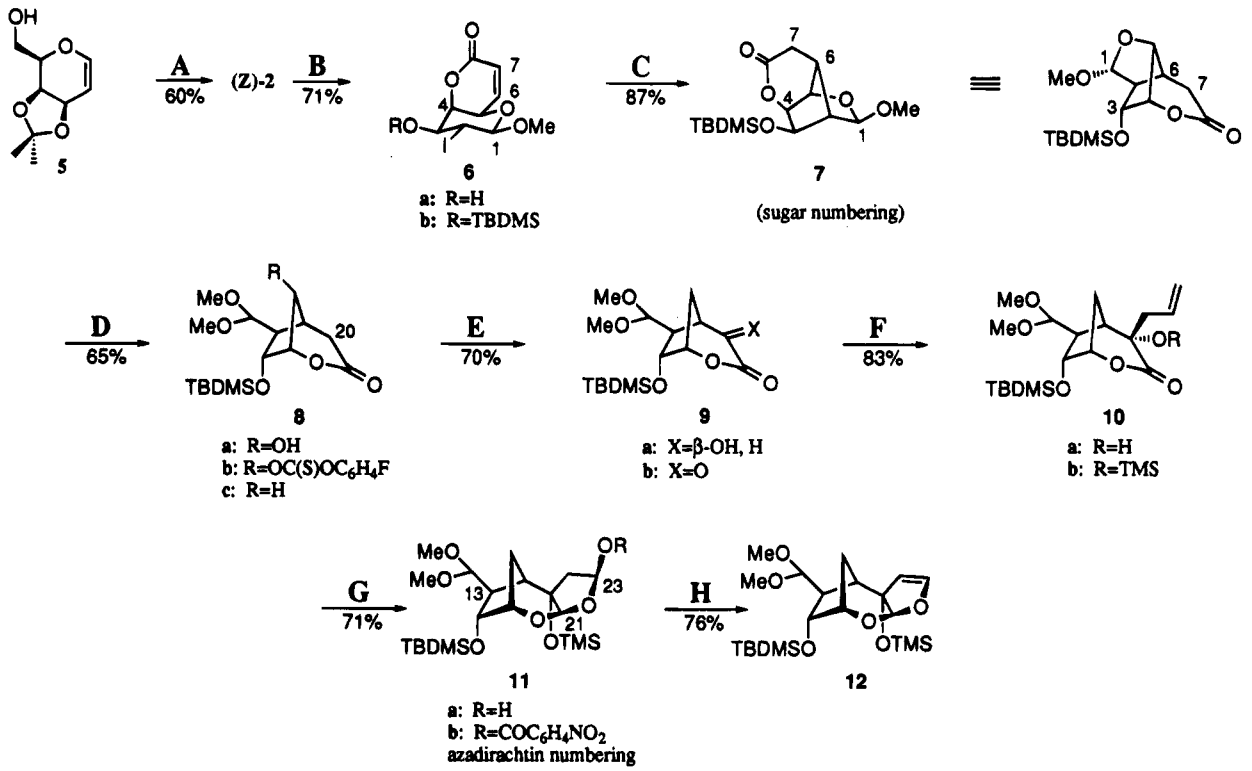
Scheme 2[a]



[a] Key: (A) (i) NIS, MeOH, CH_3CN; (ii) PCC, 4 Å MS, CH_2Cl_2; (iii) Ph_3PCHCO_2Et, MeOH (60%); (B) (i) TFA (5 equiv), H_2O (1.5 equiv), toluene; (ii) TBDMSOTf, 2,6-lutidine, THF, DMF (71%); (C) Bu_3SnH, AIBN, toluene, reflux (87%); (D) (i) PPTS, MeOH (78% + 11% SM); (ii) $ClC(S)OC_6H_4F$, NEt_3, DMAP, CH_2Cl_2; (iii) Bu_3SnH, AIBN, benzene, reflux (75%); (E) (i) KHMDS, Davis' oxaziridine; (ii) PCC, CH_2Cl_2 (70%); (F) (i) allyl-$SnBu_3$, 2 M $LiClO_4$–Et_2O; (ii) TMS-imidazole, CH_2ClCH_2Cl, 60 °C (83%); (G) (i) DIBAL, toluene, −78 °C; (ii) O_3, CH_2Cl_2; Ph_3P; (iii) $ClCOC_6H_4NO_2$, NEt_3, DMAP (71%); (H) collidine, *o*-$C_6H_4Cl_2$, reflux, 40 min (76%).

ether solution.[12,13] The stereochemistry at C(20) was dictated by attack on the *exo* face of the carbonyl,[14] and the homoallylic alcohol **10a** was isolated in 86% yield. Efficient reduction of the lactone to the lactol required protection of the α-hydroxyl group, which was accomplished using TMS-imidazole in warm dichloroethane. Reduction of the lactone with DIBAL followed, without isolation, by ozonolysis gave the "dialdehyde" (78%) which was shown by ^1H NMR to exist entirely in the tricyclic mixed acetal–hemiacetal form **11a**. Dehydration of the lactol to the desired dihydrofuran by pyrolysis of the corresponding acetates as described for more complex systems[15] was not optimal for this system, requiring temperatures in excess of 350 °C, and affording low yields. Use of the *p*-nitrobenzoate was considerably more fruitful. Thus, acylation of a 2.5:1 mixture of epimeric lactols with *p*-nitrobenzoyl chloride gave a 91% yield of a separable 10:1 mixture of *p*-nitrobenzoates (**11b**) which favored the indicated isomer. Heating **11b** in *o*-dichlorobenzene at reflux (180 °C) in the presence of a 10-fold excess of 2,4,6-collidine for 30 min gave a 76% yield of the desired dihydrofuran **12**.[16] The overall yield from 3,4-isopropylidenegalactal is 7.7% for 17 steps.

Although similar fragments have been synthesized recently,[17] this synthesis is a significant improvement in terms of its brevity and the commercial availability of the starting materials in optically pure form.[18] Furthermore, nearly all intermediates are crystalline, greatly simplifying purifications. Studies are underway to incorporate fragment **12** into a total synthesis of azadirachtin.

Supplementary Material Available: General experimental procedures and characterization data are given (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) In a related approach, Ley found that nucleophilic addition to an analogous dicarbonyl intermediate was complicated by undesired rearrangement.[17b]

(14) Stereochemistry of the addition has been determined by NOE studies on compound **11b**.

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(16) Although the minor anomeric *p*-nitrobenzoate has not yet been isolated in pure form, it has been confirmed that exposure to collidine in refluxing ODCB also effects conversion to the same dihydrofuran (**12**).

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(18) Both D-galactal ($12.50/g) and a more economical precursor, tri-*O*-acetyl-D-galactal ($3.50/g), are available from Pfanstiehl Laboratories, Waukegan, IL.